OL. VI, No. 7 SEPTEMBER, 1945

BORDEN'S REVIEW *of* NUTRITION RESEARCH

VITAMIN E IN VETERINARY AND CLINICAL MEDICINE

BORDEN'S REVIEW
of
NUTRITION RESEARCH

Reviews and summaries of research information concerning nutrition and foods. Edited by Ruth Woods. Published monthly, except July and August, by THE BORDEN COMPANY; officers of the company: Theodore G. Montague, president; E. L. Noetzel, treasurer; T. D. Waibel, secretary. Editorial office: 350 Madison Avenue, New York 17, N. Y.

VITAMIN E IN VETERINARY AND CLINICAL MEDICINE

The application of the principles of experimental vitamin E behavior* to practical problems associated with animal husbandry and clinical medicine has been somewhat confusing with respect to the results obtained. The reasons for this are manifold; experimentation with man and with domestic animals is extremely involved; controlled studies on the same individual are impossible; the widespread use in early studies of wheat germ oil concentrates of vitamin E rather than the pure vitamin has mitigated against evidence of a clear-cut nature. The mystery concerning the mechanisms by which the vitamin operates in so many diverse physiological systems is still another perplexity in the story of vitamin E and its role in the animal and human economy.

Despite this rather disappointing over-all picture, years of intensive research have brought forth some positive indications of the therapeutic value of the tocopherols (vitamin E) in human and veterinary medicine. It is expected that future research will make possible a more accurate evaluation of these findings on the basis of new knowledge uncovered and also the development of more precise methods for correctly assessing the vast amount of available data.

Veterinary Medicine:

Poultry: Experimentally, vitamin E deficiency has been shown to cause serious disturbances in the chick, exudative diathesis and nutritional encephalomalacia. Further studies with poultry on rations severely depleted in vitamin E indicate a direct correlation between vitamin E content of the hen's feed and of the eggs; and hatchability and the viability of young chicks. It is believed, therefore, that vitamin E may be a specific limiting factor in the hatchability of eggs and that one manifestation of its deficiency is a first-week embryonic mortality. Prevention of these disasters by administering vitamin E has been reported by many investigators (1, 2, 3, 4) . Inasmuch, however, as these conditions were observed on highly purified food mixtures not likely to be encountered in practical feeding, it is believed quite improbable that customary poultry mixes would ever lead, under normal conditions, to vitamin E deficiency.

Cattle: Soon after the original discovery that vitamin E deficiency is responsible for premature termination of pregnancies in the rat, Vogt-Moeller (5) and others experimented with the vitamin as a means of controlling sterility and non-infectious abortion in dairy cows. Vogt-Moeller (6) reported 75 per cent success in the treatment

---

*See *Borden's Review of Nutrition Research*, June, 1945, "Experimental Vitamin E Deficiency."

of more than 1200 sterile cows and cited other investigators who confirmed his work. The mechanism of action of the vitamin, however, remains unexplained. Studies with vitamin E as a means of combating Bang's disease in cattle (infectious abortion) have been decidedly controversial. Some success has been reported, but this has not been generally confirmed. It has been suggested that vitamin E may increase resistance to the disease organism, although conclusive evidence along these lines is lacking. Vitamin E treatment of bulls exhibiting abnormal sperm as a result of pathological changes similar to those noted in E deficient male rats has been reported unsuccessful.

More recently, experiments conducted at the Minnesota Agritural Experiment Station (7) over a period of about seven years have failed to demonstrate a need for vitamin E in the feed of cattle of either sex. Extended studies on vitamin E-free rations showed normal growth, physical and sexual development and general well-being. Likewise a carefully detailed study at Cornell University (8) failed to reveal any statistically significant difference between bulls fed vitamin-E supplemented rations and a control group with respect to production and motility of spermatozoa. No demonstrable improvement in fertility was obtained nor could a decrease in fertility of two of the animals be prevented by administration of the vitamin.

Dogs: Evidence was presented a few months ago by Elvehjem and coworkers (8a) on the importance of vitamin E in canine reproduction. In earlier experiments they had found that dogs could be successfully reared and maintained on mineralized raw milk for long periods of time. When, however, evaporated milk was fed under the same conditions, normal growth was obtained in the first generation, but all pups born of such dogs died within five days after birth. Experiments were conducted to determine the cause of the difference in reproductive ability with the two types of milk.

Early in the experiments it was noted that the first two litters born of a dog maintained on evaporated milk for several years developed a characteristic muscle dystrophy. This suggested a vitamin E deficiency and, accordingly, small amounts of the vitamin were fed the mother dog during the third gestation period. The pups born in this period did not exhibit evidence of muscular dystrophy, but all died within three days. Autopsy revealed severe intracranial and abdominal hemorrhages. The possibility that the blood-clotting factor, vitamin K, was the entity missing in the evaporated milk was next to be considered. Administration of vitamin K in other tests in addition to small amounts of vitamin E in the form of alpha-tocopherol, however, failed to prevent the fatalities. When considerably larger doses of vitamin E were administered a normal, living litter was ob-

tained. One pup in this litter developed a muscle dystrophy of the hind legs one month after birth while being nursed, but was completely cured in three weeks when transferred to raw whole milk. The remainder of the litter was completely normal and remained so after weaning, on a diet of mineralized evaporated milk. These experiments indicated that a lack of sufficient vitamin E was responsible for the inability of dogs reared on evaporated milk to successfully rear young. Animals maintained on whole milk, either raw or boiled, were successful in raising their litters. Since the limiting effect of evaporated milk did not become evident until the animals were carried through reproduction, the authors express doubt as to the practical application of their observations in human nutrition.

Sheep: Recently, Willman and associates (9) at Cornell University have reported success in treating a characteristic muscular disease of lambs, known as "stiff-lamb" disease, with wheat germ meal, alpha tocopherol, or mixed tocopherols. The disease, an ailment of young suckling lambs, is characterized by muscular stiffness. Post-mortem examination of afflicted animals revealed readily apparent gross lesions in nearly all of the skeletal muscles. In a small number of cases lesions of the heart muscle have been reported. Microscopic examination has frequently revealed extensive muscular lesions in stiff lambs whose muscles showed no gross evidence of the disease. No such lesions were found in normal lambs in the experimental group. Experiments conducted over the last fifteen years have thoroughly demonstrated that the feeding to ewes of a ration of alfalfa and cull beans, or a ration of alfalfa, cull beans, oats and barley is followed by a high incidence of the disease in the lambs. The disease does not develop in lambs whose dams are fed mixed clover and timothy hay, corn silage, oats and wheat bran. Wheat bran and wheat germ meal were found to be particularly effective in preventing the disease.

The similarity of stiff-lamb disease to the experimental muscle dystrophy encountered in vitamin E-deficient guinea pigs and other animals, together with the excellent results obtained at Cornell with wheat bran and wheat germ meal feedings, led the Cornell group to believe that the muscular disease in lambs may be a manifestation of vitamin E deficiency. Consequently, experiments were later conducted with pure tocopherols. The investigators were able to prevent the disease by feeding the tocopherols to the ewes or to the lambs after birth. Of seven stiff lambs treated, six recovered and one died. In a control group of six lambs on the disease-producing ration without vitamin E supplementation, five died and one recovered. These

studies seem to strongly indicate the importance of vitamin E as a factor in the prevention of muscular dystrophy in lambs, although the investigators point out that other factors may be involved and are continuing their studies along these lines.

Clinical Medicine:

Reproductive Disorders: Encouraged by the favorable results in treating non-infectious abortion in cattle, Vogt-Moeller later attempted similar therapy in clinical medicine. Although no direct evidence exists as to the similarity of the gestation resorption defect originally noted in E-deficient rats, with the distressing clinical anomaly of habitual abortion in women, the two conditions have symptoms in common. General health is usually good; successful mating and impregnation occur, but pregnancy is inexplicably terminated prematurely (usually within the first three months in the human). In 1931, Vogt-Moeller (10) reported results of his first two cases treated with wheat germ oil as a source of vitamin E. One of the patients had a history of four, unexplained spontaneous abortions; the other, of five. Following treatment with vitamin E during their next pregnancies, each of the women gave birth to a healthy, full-term child. Whether, after a history of repeated spontaneous abortions, in the absence of any recognizable causative anatomic or physiologic abnormalities, these and other women would have eventually had successful births without vitamin E treatment is an interesting speculation which must be taken into account in evaluating reports of vitamin E therapy.* During the following eight years Vogt-Moeller treated several hundred patients with histories of habitual abortion and reported a total average of 75-80 per cent success (6). He points out that this percentage of success is probably higher than that which might be expected in the absence of treatment with vitamin E.

In contrast to Vogt-Moeller's studies, Shute (12) reports little success in the treatment of habitual abortion with vitamin E, but an average of 68 per cent success in the treatment of "threatened" abortion (signs of impending abortion, such as vaginal bleeding during early pregnancy). Watson and Tew (13, 14) have reported success in 34 of 46 cases of habitual abortion and indicate also the value of vitamin E therapy in threatened abortion. Currie (15) reported even more highly favorable results – 23 normal births out of 24 cases in which the aggregate 73 previous pregnancies had resulted in only six healthy living children. A few months later, another paper by Vogt-Moeller (16) reported successful delivery in 38 out of 52 pa-

*According to Malpas (11), after one, two or three successive spontaneous abortions the statistical chances of the next pregnancy being carried to term are 78, 62 and 27 per cent, respectively.

tients with a history of repeated spontaneous abortion between the second and seventh months. Four years later, in 1940, Collins *et al* (17) contributed additional favorable reports concerning the prophylactic value of wheat-germ oil in cases of threatened and habitual abortion. In a group of patients showing evidence of possible abortion, 87 per cent were prevented from aborting, while in the habitual abortion group, twelve patients who had previously had a total of 21 pregnancies with only three live births, produced eight living children. Encouraging results were likewise reported, for a small group of patients, by Lubin and Waltman (18) in the following year.

In 1943, Silbernagel and Burt (19) presented an interesting report comparing the effectiveness of vitamin E therapy with that of other routine measures (including bed rest, sedatives, hormones) in preventing premature termination of pregnancy. Their studies covered 140 patients having had a total of 870 threatened abortions in previous consecutive pregnancies. In a control group of 50 patients treated solely by general methods such as bed rest, sedatives, ice bags, only 6 per cent went to term; in another group treated with special hormone preparations, 18.2 per cent went to term; in a third group treated with various types and combinations of vitamin E preparations, from 16.7 to 85.7 per cent went to term. The most effective results with different vitamin E preparations were obtained with a combination of alpha-tocopherol administered intramuscularly and a mixture of natural tocopherols given by mouth. This treatment was successful in more than 85 per cent of the cases involved.

Threatened and habitual abortion in women constitutes a problem which is, despite the many favorable reports of therapy with vitamin E preparations, not merely nutritional, but largely medical in scope. A possible vitamin E deficiency is only one of many factors contributing to the disorder. Endocrinological factors, particularly, have been found to be intimately involved in these conditions. In many instances success equal to or even greater than that obtained with vitamin E has been obtained with corpus luteum hormone preparations administered alone or in conjunction with the vitamin. Any critique of vitamin E therapy, therefore, cannot properly be made without careful consideration of the influence and interaction of these other factors. At the present time, the therapeutic value of vitamin E in human abortion is not conclusively established, although strong presumptive evidence for its efficacy exists. For this reason, vitamin E is customarily used, on an empirical basis, in current obstetrical practice when indicated.

Vitamin E therapy has been reported successful in the treatment of certain other obstetrical disorders including premature separation

of the placenta, late toxemias and symptoms of impaired kidney function such as albuminuria, edema and elevated blood pressure (12, 20, 21). It is generally believed to be without effect, however, in cases of actual sterility, that is where fertilization and impregnation fail to occur, although a recent report by Shute (22) has indicated success in stimulating human spermatogenesis with resultant conception in 37 per cent of 27 sterile couples of which the male received a daily dose of 10 milligrams of alpha-tocopherol for two weeks.

Neuromuscular Disorders: The case for vitamin E in the treatment of neuromuscular or muscular disorders rests on somewhat flimsy evidence. Because of early reports, particularly those of Einarson and Ringsted (23) describing specific lesions in the nervous systems of vitamin E deficient experimental animals, great interest and hope were aroused in the possibilities of the clinical use of vitamin E for treating various chronic degenerative diseases of the nervous system. Chief among these was the progressive, fatal disease known as amyotrophic lateral sclerosis, the disease responsible for the death of baseball's Lou Gehrig. Numerous clinical reports have appeared within the past four or five years, but a great majority of these have presented discouraging results (24). Among the earliest to use vitamin E in neuromuscular diseases was Bicknell (25). He treated four patients having amyotrophic lateral sclerosis with dried whole wheat germ. Of these, one improved slightly, another was almost entirely cured and two eventually died. Good response to treatment, but not complete cure, was obtained in a series of eighteen patients with various other muscular dystrophies who were treated with a similar wheat germ preparation.

Conflicting results with respect to the response of neuromuscular diseases to treatment with vitamin E in the form of alpha-tocopherol concentrates have been reported (26, 27, 28, 29). Wechsler (27) suggests that successful treatment is dependent upon the administration of sufficiently large doses of the vitamin and postulates, further, that there are several types of the same neuromuscular disease only one of which responds to vitamin E therapy. An interesting report by Davison (29) indicates the possibility that certain pathological tissue changes in the nerves and muscles may respond to treatment with vitamin E, although the reversal of such pathological changes was not extensive enough to permit improvement or even to prevent ultimate death from the disease. Similar conclusions are suggested by the work of Gutierrez-Mahoney (30). In addition, he presents the theory that since vitamin E is so essential to the rapidly developing young of experimental animals, it may be a factor in

infantile cerebral palsy. The disorder may arise, he suggests, as a result of maternal vitamin E deficiency during pregnancy. The importance of vitamin E in certain muscular disturbances of infancy and childhood is further indicated by the studies of Stone (31) who obtained favorable results with vitamin E therapy in several cases.

Reports on the treatment of degenerative muscle disorders, in which there is no involvement of the nerves, have been somewhat less discouraging than those concerning neuromuscular diseases. In general, the various forms of muscular dystrophies and atrophies (muscle degeneration due to defective muscle metabolism) have not responded too well to vitamin E therapy. Multiple sclerosis, a disease characterized by the occurrence of hardened patches in the brain and spinal cord resulting in paralysis, tremors, apoplectic reactions or speech disturbances, has responded favorably, in one instance (32) to treatment with vitamin E following therapy with vitamin B complex and quinine. Most encouraging results have been reported with respect to the treatment of fibrositis (a form of rheumatism) in 173 of 175 patients, complete relief being obtained within one to three weeks following administration of wheat-germ oil or the various tocopherols (33, 34). Wheat-germ oil in conjunction with heat treatment, hormones and vitamin B complex has also been reported effective in alleviating the pain of atrophic arthritis in seventeen of twenty-two cases (35). The evidence presented to date, however, still remains somewhat insufficient for the definite establishment of vitamin E as a therapeutic agent in these diseases. Mason (36) has summarized the situation briefly as follows:

> "Although no clinical myopathy* or neuropathy* yet explored has proved to be a counterpart of the nutritional muscular dystrophy of laboratory animals, . . . hope still exists that vitamin E will eventually find a valuable application to clinical medicine."

The experimental background of vitamin E and its relation to neuromuscular disorders has been outlined in an excellent review by Pappenheimer (37) which appeared some years ago. A concise summary of actual experience with the vitamin in clinical medical practice appeared in another review during 1944 (38).

Mechanism of Vitamin E Action:

Perhaps the least understood, most provocative phase of vitamin E behavior is that pertaining to its mode of action in the animal body. Experimental vitamin E deficiency may be manifested by sterility and gestation-resorption in rats, muscle paralysis in guinea pigs and other animals, and by exudative diathesis and brain lesions in the

---

*Any disease of the muscles or nerves, respectively.

chick.† Because of the accepted principle of specificity of vitamin action, it has been suggested (39) that all of these apparently unrelated effects may be due to a single basic function of the vitamin. It is believed by a number of investigators that the outstanding chemical property of the tocopherols, their anti-oxidant behavior, may be the common denominator in explaining their physiological behavior. Important as this antioxidant function may be, however, it cannot represent the prime role of vitamin E in the animal body according to Mason (36) who cites the following reasons:

1. The inability of other antioxidants to substitute for vitamin E.
2. The inverse relationship between antioxidant and biological actions of alpha-, beta-, and gamma- tocopherols.
3. Lack of evidence that tocopherols retain their antioxidant activities after their ingestion.
4. The manner in which changes unrelated to the phenolic hydroxl group in the molecule (the group responsible for the antioxidant behavior) alter biological activity of the tocopherols.

There has been no dearth of alternative theories offered in explanation of the physiological action of vitamin E. While none of these has received sufficient corroboration to establish it as valid, the suggestions put forth are of considerable interest as possible avenues for future research. With respect to its role in muscle metabolism, for example, the suggestion has been made (40) that tocopherols, probably in phosphorylated form and acting through some as yet unknown enzyme system (much like thiamine and cocarboxylase), serve to inhibit or regulate the oxidative process. In their absence, it is presumed the oxidative processes get out of control and allow the muscle to be "consumed in its own fire." Another theory based on the irrevocable cell changes noted in the rat testis, postulates that vitamin E may be required either for the synthesis of nuclear chromatin, the basic framework of cell structure, or for the maintenance of the integrity of this material (41). The possible relation between vitamin E and the synthesis of nucleoproteins is hinted at in the case of arginine* deficiency which in man may result in a rapid reduction in sperm count and in rats cause a testicular degeneration similar to that produced by lack of vitamin E. A great deal of speculative material has also been reported concerning possible interrelationships between arginine and creatine metabolism as influenced by vitamin E, but these are all hypothetical suggestions demanding considerable future research before they can be evaluated.

---

†cf. *Borden's Review of Nutrition Research,* June, 1945, "Experimental Vitamin E Deficiency."

*The nucleoproteins, especially those of mature sperm, are characterized by an exceptional content of the amino acid, arginine (36).

The relation of vitamin E to the fat content of the diet and to fat metabolism in general is another promising field of investigation which may eventually offer a clue to the action of the vitamin. The antioxidant theory of vitamin E activity is closely tied in with the interrelationships in fat metabolism, as well as with the theory of control of oxidative processes in the muscle. The unique sparing action of vitamin E with respect to vitamin A and its precursor, carotene, (42, 43) both of which are highly susceptible to oxidative destruction in the presence of unsaturated fatty acids, seems to offer another support for the antioxidant theory. For example, it has been shown experimentally that vitamin E increases liver storage of vitamin A (44); this has been interpreted, as a result of additional experimental findings by Hickman *et al* (45) as evidence of an antioxidant action of the tocopherols in the intestinal tract.

Finally, the effect of the presence or absence of non-vitamin dietary components other than vitamin E* in causing or preventing symptoms of vitamin E deficiency cannot be overlooked in seeking an explanation of the mode of behavior of this vitamin. These components are thought to affect the physiological state of the susceptible tissues in such a way as to make them either more resistant or more sensitive to the lack of vitamin E.

Present evidence, provocative as it may be, is still insufficient, however, to permit a decision as to whether the tocopherols have a single, basic function or a multiple function in the animal body. Even more nebulous is the concept of what such function or functions may be, although the scattered clues thus far available hold forth the promise of an early solution to this question with continued future research.

Conclusion:

It is apparent that clinical and even experimental investigations concerning vitamin E are still in the early stages of speculation and exploration. The precise biological role that the vitamin plays in the economy of the animal body still remains an elusive problem, although the answer seems to be near at hand. As Mason (36) has remarked:

> "What have seemed for many years to be irreconcilable findings now seem to fit into some more rational pattern. In fact, the structural and bio-

---

*For example: increasing the concentration of soluble salts; addition of histamine in the presence of dietary fat; addition of fat, cholesterol or unsaturated fatty acids; or increasing carbohydrates and decreasing proteins will precipitate vitamin E deficiency symptoms in the chick. Addition of lipocaic or inositol, both lipotropic materials, prevents the disturbances although choline (also lipotropic) does not (46, 47, 48). (*For discussion of choline and lipotropic substances, see Borden's Review of Nutrition Research,* October, 1942.)

chemical alterations characterizing the manifestations of vitamin E deficiency in a wide variety of animal types, largely by virtue of their striking dissimilarities, have served as important landmarks guiding investigators toward a common focus encompassing many new problems for future investigation. It appears that these will center around the relations of tocopherols to the absorption and utilization of lipids, to products formed in the intermediary metabolism of fats (perhaps carbohydrates and proteins also), and to oxidative mechanisms essential to the structural and functional integrity of muscles and other tissues."

With respect to the clinical significance of vitamin E, it can merely be said that it possesses potential, although as yet definitely unproved, value in certain muscular diseases and a somewhat more secure position in the therapy of various human reproductive disorders, particularly habitual and threatened abortion. In the field of veterinary medicine, the evidence is predominantly on the negative side with respect to vitamin E therapy of sterility and abortion in cattle and pigs. There is some evidence as to the effectiveness of the vitamin in the treatment of a characteristic muscle disease in lambs.

With the availability of the pure tocopherols it is now possible to repeat many of the early laboratory and clinical experiments in which crude wheat germ oil concentrates were used, and thereby permit a more precise estimation of the potentialities and limitations of this promising member of the vitamin family.

REFERENCES CITED

1. ADAMSTONE, F. B. The effects of vitamin E deficiency on the development of the chick. J. Morph. and Physiol. *52*, 47 (1931).

2. CARD, L. E. Poultry Science *8*, 328 (1929).

3. BARNUM, G. L. The vitamin E content of eggs as related to the diet of the hen and hatchability. J. Nutr. *9*, 621 (1935).

4. ENDER, F. Ueber die Bedeutung des E-vitamins für die Hühnnerzucht. Ztschr. für Vitaminforsch. *4*, 106 (1933).

5. BAY, F. and P. VOGT-MOELLER. Continued studies on treatment of sterility in cows and breeding sows with wheat-germ oil (vitamin E). Veterinary J. *90*, 288 (1934).

6. VOGT-MOELLER, P. The therapeutic employment of vitamin E in human and veterinary clinical medicine, in *Vitamin E — A Symposium*, Food Group (Nutrition Panel), Soc. Chem. Inc., London (1939).

7. GULLICKSON, T. W., L. S. PALMER, W. L. BOYD and F. C. OLSON. Vitamin E in the nutrition of cattle. J. Dairy Science *27*, 634 (1944).

8. SALISBURY, G. W. A controlled experiment in feeding wheat germ oil as a supplement to the normal ration of bulls used for artificial insemination. J. Dairy Science *27*, 551 (1944).

8a. ELVEHJEM, C. A., J. E. GONCE and G. W. NEWELL. The effect of vitamin E on reproduction in dogs on milk diets. J. Ped. *24*, 436 (1944).

9. WILLMAN, J. P., J. K. LOOSLI, S. A. ASDELL, F. B. MORRISON and P. OLAFSON. Prevention and cure of muscular stiffness ("stiff-lamb" disease) in lambs. J. Animal Science *4*, 128 (1945).

10. VOGT-MOELLER, P. Treatment of habitual abortion with wheat-germ oil (vitamin E). Lancet *2*, 182 (1931).

11. MALPAS, P. A study of abortion sequences. J. Obstet. Gynecol. Brit. Emp. *45*, 932 (1938).

12. SHUTE, E. A diagnosis and treatment of vitamin E deficiency, in *Vitamin E—A Symposium*, Food Group (Nutrition Panel), Soc. Chem. Ind., London (1939).

13. WATSON, E. M. and W. P. TEW. Wheat-germ oil (vitamin E) therapy in obstetrics. Trans. Am. A. Obstet., Gynecol. and Abd. Surg. *48*, 189 (1935).

14. WATSON, E. M. Clinical experiences with wheat germ oil (vitamin E). Canad. Med. Assoc. J. *34*, 134 (1936).

15. CURRIE, D. W. Vitamins for habitual abortion. Brit. Med. J. *1*, 752 (1936).

16. VOGT-MOELLER, P. Die Behandlung des habituellen aborts mit weizenkeimöl (E vitamin) Klin. Wochenschur. *15*, 1883 (1936).

17. COLLINS, C. G., J. C. WEEK and J. H. COLLINS. The treatment of spontaneous threatened or habitual abortion. Surg. Gynec. & Obstet. *70*, 783 (1940).

18. LUBIN, S. and R. WALTMAN. The use of synthetic vitamin E in the treatment of abortion. Am. J. Obstet. & Gynecol. *41*, 960 (1941).

19. SILBERNAGEL, W. M. and O. P. BURT. Threatened abortion; results of treatment in 140 cases. Ohio State Med. J. *39*, 430 (1943).

20. SHUTE, E. The early diagnosis of abruptio placentae and its treatment with wheat-germ oil. Am. J. Obstet. & Gynecol. *33*, 429 (1937).

21. SHUTE, E. The effect of vitamin E upon impaired kidney function. Preliminary note. Canad. Med. Assoc. J. *52*, 151 (1945).

22. SHUTE, E. The effect of vitamin E upon sperm. Urol. & Cutan. Rev. *48*, 423 (1944).

23. EINARSON, L. and A. RINGSTED. *Effect of chronic vitamin E deficiency on the nervous system and the skeletal musculature in adult rats.* Oxford Univ. Press, London (1938).

24. ZECH, V. L. and I. R. TELFORD. Negative therapeutic effect of massive doses of vitamin E on amyotrophic lateral sclerosis. Arch. Neurol. Psychiat. *50,* 190 (1943).

25. BICKNELL, F. Vitamin E in the treatment of muscular dystrophies and nervous diseases. Lancet. *1,* 10 (1940).

26. WECHSLER, I. S. Recovery in amyotrophic lateral sclerosis treated with tocopherols (vitamin E); preliminary report. J. Am. Med. Assoc. *114,* 948 (1940).

27. WECHSLER, I. S. Amyotrophic lateral sclerosis treated with synthetic vitamin E. Arch. Neurol. & Psychiat. *45,* 873 (1941).

28. FERREBEE, J. W., W. O. KLINGMAN and A. M. FRANTZ. Vitamin E and vitamin B_6; clinical experience in the treatment of muscular dystrophy and amyotrophic lateral sclerosis. J. Am. Med. Assoc. *116,* 1895 (1941).

29. DAVISON, C. Effect of vitamin E therapy on the central nervous system in amyotrophic lateral sclerosis. Am. J. Path. *19,* 883 (1943).

30. GUTTIERREZ-MAHONEY, W. DE. Neural myatrophy and vitamin E. South Med. J. *34,* 389 (1941).

31. STONE, S. Vitamin E in the treatment of muscle disorders of infancy and childhood. J. Ped. *18,* 310 (1941).

32. RAMSEY, F. M. Multiple sclerosis. Med. Woman's J. *48,* 289 (1941).

33. STEINBERG, C. L. Vitamin E in the treatment of fibrositis. Am. J. Med. Sciences *201,* 347 (1941).

34. STEINBERG, C. L. The tocopherols (vitamin E) in the treatment of primary fibrositis. Ann. Int. Med. *19,* 136 (1943).

35. STONE, S. The neurological and endocrine aspects of atrophic arthritis (deformans); report on the use of vitamin E and artifical fever. J. Nerv. and Mental Dis. *97,* 693 (1943).

36. MASON, K. E. Physiological action of vitamin E and its homologues, in *Vitamins and Hormones,* Vol. 2, Academic Press, New York (1944).

37. PAPPENHEIMER, A. M. Muscular disorders associated with deficiency of vitamin E. Physiol. Rev. *23,* 37 (1943).

38. ANON. Vitamin E; History, physiologic actions and therapeutic uses. Roche Review *9,* 77 (1944).

39. ANON. Vitamin E as a physiologic antioxidant. Nutr. Rev. *3,* 17 (1945).

40. HOUCHIN, O. B. The *in vitro* effect of alpha-tocopherol and its phosphate derivative on oxidation in muscle tissue. J. Biol. Chem. *146,* 313 (1942).

41. MASON, K. E. Difference in testis injury and repair after vitamin A deficiency, vitamin E deficiency and inanition. Am. J. Anat. *52,* 153 (1933).

42. HICKMAN, K., M. KALEY and P. HARRIS. Covitamin studies. I. The sparing action of natural tocopherol concentrates on vitamin A. J. Biol. Chem. *152,* 303 (1944).

43. HICKMAN, K., M. KALEY and P. HARRIS. Covitamin studies. III. The sparing equivalence of the tocopherols and mode of action. J. Biol. Chem. *152,* 321 (1944).

44. MOORE, T. The effect of vitamin E deficiency on the vitamin A reserves of the rat. Biochem. J. *34,* 1321 (1940).

45. HICKMAN, K., P. HARRIS and M. WOODSIDE. Interrelationship of vitamins A and E. Nature *150,* 91 (1942).

46. DAM, H. and J. GLAVIND. Factors influencing capillary permeability in the vitamin E deficient chick. Science *96,* 235 (1942).

47. DAM, H. and E. M. KELMAN. The effect of vitamin E in the blood plasma lipids of the chick. Science *96,* 430 (1942).

48. DAM, H. Effect of cod liver oil and rancidity on certain vitamin E deficiency symptoms. Proc. Soc. Exp. Biol. Med. *52,* 285 (1943).